Liquid based cytology in cervical cancer screening

Is as sensitive as conventional cytology, and has other advantages

SATURN STILLS/SPL

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Cervical screening has been shown to reduce the incidence of cervical cancer, but only in the setting of well organised, high quality programmes. In the United Kingdom the NHS cervical screening programme has been estimated to prevent around 80% of deaths from cervical cancer.[1]

Liquid based cytology represents the first major change in preparation method for cervical screening samples for over 50 years. Instead of cells being smeared onto a glass slide, they are washed into a vial of liquid and filtered, and a random sample is presented in a thin layer on a glass slide. These slides can then either be screened by skilled staff or subjected to partially automated imaging. The process is being widely used in the United States, many European countries, and elsewhere.

In this week's *BMJ* two studies compare the accuracy of liquid based cytology with conventional cytology.[2,3] The randomised trial by Ronco and colleagues found no significant difference in sensitivity for cervical intraepithelial neoplasia of grade 2 or more with liquid based cytology using ThinPrep (Cytyc, Boxborough, MA, USA) compared with conventional cytology.[2] However, more false positive results were found with liquid based cytology, leading to a lower positive predictive value. The observational study by Davey and colleagues compared the accuracy of the automated ThinPrep imaging system to that of conventional cytology, using split sample pairs (the ThinPrep sample was obtained after the conventional one in a single collection).[3] The ThinPrep Imager detected 1.29 more cases of histological high grade squamous disease per 1000 women screened than conventional cytology, where cervical intraepithelial neoplasia grade 1 was the threshold for referral to colposcopy.

What do these results add to what is already known? Several manufacturers have developed liquid based cytology systems. The literature evaluating them is extensive and varied. Most are observational studies, either split sample studies or studies comparing outcome with previous outcomes at the same laboratory.[4] Several national screening programmes and bodies such as the Food and Drug Administration have evaluated the evidence for liquid based cytology and come to different conclusions,[5,6] although most evaluations have led to implementation. Of the few randomised controlled trials, those considered to be of high quality have tended to show no difference in sensitivity with liquid based cytology.[7]

This wealth of conflicting data presents difficulties for screening programmes worldwide, trying to make decisions on implementation in their own setting. Cervical screening has had varying levels of success in different countries. Rates of inadequate conventional smears vary from 9.5% in the United Kingdom to <1% elsewhere. Detection rates for abnormalities vary as well (even after differences in terminology are taken into account) and are influenced by sensitivity of screening, incidence of disease in the population, coverage of the population, age of starting screening, and screening interval—all factors that vary between countries. The UK has one of the highest sensitivities for detecting abnormality in a single conventional smear,[8] one of the longest screening intervals (three or five years, depending on age), and high population coverage (over 80%). In other countries women may have smears taken every six months, and screening every 12-24 months is common. The UK has rigorous training and quality assurance and is the only country with a policy of rapidly rescreening 100% of negative and inadequate samples.

These variables mean that results of the most rigorous study in one setting may not be directly applicable in another. Factors such as training of laboratory staff and the people who take samples, which may have a major effect, have been overlooked in several otherwise well designed trials. The manufacturers of liquid based cytology systems have mandatory training courses, but in the UK a much more lengthy and controlled training process is undertaken by training centres approved by the NHS cervical screening programme. Trainers in the UK have noted that performance improves during and after training, suggesting that sensitivity will be increased, but this has not been formally evaluated. The quality and duration of training specific to liquid based cytology may have an impact on detection rate, and this could contribute to the differing outcomes in reported studies.

The imager study by Davey[3] is exciting because a significant increase in sensitivity has been robustly shown, and the authors also found a dramatic increase in screening productivity (the number of slides screened per hour by a single member of staff).[9] However, this must be interpreted with caution, because the outcome could be different elsewhere. Controlled trials of automated systems compared with liquid based cytology alone are under way in other national settings.[10]

Introduction of liquid based cytology to the UK will be complete during 2008. This follows an evaluation of the available evidence by the National Institute of Health and Clinical Excellence, which concluded that liquid based cytology was as sensitive as conventional cytology, and commissioned an implementation pilot.[11] Increased sensitivity was not the aim of implementing

liquid based cytology in the UK, but in laboratories that have converted to liquid based cytology, specificity has been maintained,[12] and detection rate may have increased.[13] The desired end points in the UK—to reduce the rate of inadequate samples and increase screening capacity—have been achieved, and at least some of the additional cost of liquid based cytology has been offset by fewer repeat tests. Liquid based cytology also gives a platform for human papillomavirus testing, automation, and other new technologies, and is popular with staff. Women benefit from faster reports and less anxiety.

Is liquid based cytology superior to conventional cytology? The answer is yes, but sensitivity is not the reason for this superiority, or at least not the only one. The addition of automation may make liquid based cytology even better.

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The future role of the Department of Health

Will the new health secretary translate political rhetoric into reality for the NHS?

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Among the many papers competing for the attention of Alan Johnson, the new secretary of state for health, the one that calls out for priority is the report of a Cabinet Office team on the "capability" of the Department of Health.[1] The report, one of a series of reviews ranging across Whitehall, is highly critical. The DH is not alone in attracting criticism; unsurprisingly the review of the Home Office was more scathing still, and no government department has emerged from the reviews as a flawless instrument for framing and executing ministerial policy. But the timing of the report's publication poses a challenge for Mr Johnson as he takes over as health secretary. The challenge is to decide just what kind of competence he wants his department to develop, and in turn what the department's role should be.

In a foreword to the capability review, the trio of officials at the top of the department—the permanent secretary, the NHS chief executive, and the chief medical officer—welcome its findings, inasmuch as these will add "focus and momentum" to what they are doing already. Two of the three are relatively new to their posts and may well welcome the extra leverage the report gives them in introducing change. And change is clearly needed. The following selection conveys the key points. Morale within the DH as well as within the NHS is low: "the pace at which change has been implemented has led to a sense of disenfranchisement among staff and delivery partners," the report argues. The quality of briefing to ministers has diminished in some areas. Further, "policies tend to be developed in organizational silos and cross-boundary integration issues are not routinely thought through" with the result that "tensions between individual well-intended policies" emerge during implementation. Sufficient emphasis is not always placed on planning how policy will be implemented. And "there is a need for more consistent engagement between the Department and front-line staff."

Some of the flaws diagnosed by the review have a long history: many organisational permutations have tried to overcome the problem of policy silos.[2] But others reflect the DH's more recent transformation from a traditional civil service department into a new managerial model "focused on delivery of political objectives rather than policy or risk analysis, weak in policy research capacity but willing to respond to central direction," as a recent study argues.[3] As of May 2006, only one of the top 32 officials in the DH was a career civil servant, whereas 18 came from the NHS and six from the private sector. The shift has been from those who saw their role as being to save ministers from themselves, to those who saw it as being to deliver results. If the pathology of the former approach was conservative obstructionism, that of the latter was a readiness to run with even the silliest ministerial initiative.

Other factors, too, have been at work. The staff of the DH has been cut by half. Institutional memory has suffered as the knowledge of what did or did not work in the past has been dispersed; policy work has

been farmed out to consultants, with mixed results. But central to the changes has been the emphasis on delivery. The DH scores well on delivery in the capability review, with the usual litany of waiting time and other targets achieved. The emphasis on delivery—and the accompanying culture of target setting—has meant developing the ability of central government to monitor and, if need be, intervene in local performance.[4] The DH has done this in spades. But now, as the review points out, "The Department needs to lead the next stage of transition in the NHS from top-down performance management to locally driven healthcare systems."

Will the new secretary of state accept the logic of "locally driven healthcare systems" and accept diversity in the pursuit of national policies? If he does, the DH can develop the competencies required for a more policy oriented role, so avoiding a repetition of recent policy fiascos, such as new medical contracts which managed to attract widespread criticism of excessive generosity—of paying more for less work—while still leaving the profession in a state of tetchy unhappiness. The point remains relevant whatever happens about the future governance of the NHS.

The case for some kind of independent board for the NHS combines two distinct arguments.[5] The first is that such a board would insulate the NHS from day to day political interference; the second is that it would insulate the NHS from intrusive central direction. The two are not necessarily linked: an independent board could be just as directive as any government department. So the crucial question is whether Mr Johnson will translate the political rhetoric about locally driven health care and the empowerment of NHS professionals into reality.

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Advising patients on dealing with acute chest pain

Instructions about using GTN and when to call an ambulance need to be clearer

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How long people with chest pain should wait before calling an ambulance is a question familiar to general practitioners and emergency doctors. The answer is complicated by the use of sublingual nitrate sprays, which promptly relieve the pain of stable angina.[1] Ideally, patients would be able to distinguish stable angina from a potentially life threatening acute coronary syndrome, but in reality they do not. Therefore the decision about when to call an ambulance needs to balance between an overly cautious strategy that could overburden emergency medical services and one where delayed action leads to higher morbidity and mortality. The balance is difficult to find because international guidance indicates that consensus has not been reached, even among cardiologists.[2-4]

The British Heart Foundation advises patients with known ischaemic heart disease that chest pain that lasts more than 15 minutes is probably a heart attack.[2] Within this time patients are advised to use their glyceryl trinitrate (GTN) spray three times at five minute intervals before calling an ambulance. Yet a recent British Heart Foundation campaign advises members of the general public with potential "de novo" chest pain (a lower risk population) that "A chest pain is your body saying call 999. Doubt kills—call 999 immediately."

Campaigns aimed at the general population have been unsuccessful in reducing mortality from acute coronary syndromes.[5 6] However, no studies have examined the effect solely in people at high risk—those with an established diagnosis of ischaemic heart disease and those with established cardiovascular disease or risk factors for cardiovascular complications[7]—and the potential of sublingual nitrates to prompt a rapid, appropriate response (in turn reducing mortality and morbidity associated with late presentation).

The European Society of Cardiology does not offer precise guidance; it simply advises "carefully instructing patients on the use of short acting nitroglycerin."[5] The recommendations of the American College of Cardiology and American Heart Association were previously in line with the British Heart Foundation. However, updated guidelines in 2004 encouraged patients with symptoms suggesting ST elevation myocardial infarction (STEMI) to contact emergency medical services earlier. They now recommend "one GTN spray and 5 minutes" before calling an ambulance.[6]

Manufacturers of nitrate sprays also give varying and sometimes non-specific instructions regarding the dose, such as "No more than three metered doses at any one time and a minimum of 15 minutes between consecutive treatments." Therefore, the onus is on the prescribing doctor to guide the patient.

The evidence for early presentation and treatment of STEMI has long been established. Necrosis of viable myocardium predominantly occurs between 30 to 90 minutes after coronary artery occlusion. This has formed the basis of "the golden hour" during which prompt reperfusion strategies (thrombolysis or primary angioplasty) prevent extensive myocardial necrosis that leads to left ventricular dysfunction and worse prognosis. Even before angioplasty became widely used, thrombolysis within the first hour cut deaths by half.[8] This led to the advent of prehospital thrombolysis and "call to needle" targets, which are generally being met.

If the patient has a cardiac arrest out of hospital, early attention from a paramedical team with a defibrillator is life saving, but the chance of successful defibrillation declines 7-10% each minute after cardiac arrest.[9] One early study of out of hospital cardiac arrest showed that the median time from onset of symptoms to cardiac arrest was 10 minutes.[10] Clearly, waiting 15 minutes, as the British Heart Foundation suggests,[2] will be too long for some patients.

Recent data on sudden cardiac death do not confirm the early series; the symptoms were present for a median of 30 minutes before ventricular fibrillation started.[11] However, the data do confirm that most sudden cardiac deaths occur in patients with known cardiac disease, at home, and in the presence of relatives. This reaffirms the importance of clear and precise education for patients and relatives.

Most acute coronary syndromes occur in people already known to have ischaemic heart disease or to be at high risk. In this group the risk of subsequent myocardial infarction or death is 5-7 times higher than in the general population, and at least 70% of deaths from coronary heart disease occur in people who have had previous manifestations of cardiovascular disease.[12] However, recent data have shown that 40% of the general population would not immediately call an ambulance during a suspected myocardial infarction, and the greatest delays in calling 999 are in people at high risk.[13] The obvious implication is that people at high risk are not receiving clear, effective guidance despite receiving care from a doctor at some stage.

The advent of rapid access chest pain clinics, patient information leaflets, and cardiac rehabilitation clinics may have made the medical community complacent about face to face doctor-patient counselling. However, any clinician faced with a patient with existing ischaemic heart disease should be able to give clear and precise instructions about when to call an ambulance.

On the basis of the pharmacodynamics of sublingual nitrates and the benefit of early presentation, we advise patients with known ischaemic heart disease or at high risk of myocardial infarction to carry a GTN spray at all times and, should they develop acute chest pain, to take two metered doses (800 µg) immediately. If the pain persists at five minutes they should call an ambulance. They should not waste time by first calling a friend or relative and should not drive themselves to the emergency department.[14 15] Patients and their relatives should also be taught how to recognise high risk features of chest pain, such as increasing frequency and severity of attacks (unstable angina), and autonomic features (common in STEMI).

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Prevention of HIV by male circumcision

Effective but integration with existing sexual health services remains the biggest challenge

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Three randomised controlled trials consistently show that medically performed male circumcision can reduce the acquisition of HIV infection in men by at least 50%.[1-3] In east Africa and southern Africa—where rates of new HIV infections are high and circumcision rates are low—modelling studies estimate that circumcision could reduce the incidence of HIV in men by 50-60%.[4 5] Clearly, the size of this effect would be determined by uptake. If uptake were 100%, an estimated 2 million new infections and 0.3 million deaths in sub-Saharan Africa would be averted over 10 years, and up to 5.7 million new infections would be averted over 20 years.[6] In a setting like Orange Farm in South Africa where one of the trials was performed,[1] a 50% uptake of male circumcision could avert 32 000-53 000 new infections over 20 years. Conclusions about the effect of male circumcision on the acquisition of HIV in women are awaiting the completion of a trial in Rakai, which is expected in 2008.[7]

Countries face many challenges as they consider policies on circumcision for preventing HIV, especially as a surgical intervention in healthy men for preventing an infectious disease is a new paradigm in public health.

The United Nations AIDS/World Health Organization guidance on scaling up male circumcision is a useful starting point at a country level.[4] It advises that male circumcision should be included as part of a comprehensive package of HIV prevention; health services in developing countries should be strengthened to provide high quality circumcision services; and that circumcision should be targeted in populations with low circumcision rates and high HIV prevalence at no cost to the client.[4]

Uptake will be socially complex as circumcision involves aesthetic changes to the penis that impact on perceptions of masculinity, religious practices, and rites of passage for boys to manhood in many African cultures. Also, an intervention where healthy men undergo an irreversible surgical procedure that carries about a 10% complication rate makes informed consent for the procedure extremely important. The consent process will have the added benefit of providing an opportunity for integrating counselling on safer sex practices and of enhancing strategies for HIV risk reduction at the individual level.

How to integrate this intervention into existing services is a major challenge in these settings. Health services for people who would benefit most from this intervention are already under strain from years of underfunding and neglect, as well as the impact of the AIDS epidemic. To offer safe circumcision on the scale needed to affect the transmission of HIV within communities, investment is needed for training healthcare workers; developing surgical facilities; obtaining surgical supplies, especially suture material; and sterilising surgical equipment.

In addition, preliminary data from the ongoing trial in Rakai suggest an excess risk of HIV transmission in women from circumcised men who are infected with HIV, perhaps because sexual intercourse is resumed before the wound has fully healed. Therefore, until more definitive data are available, men should be tested for HIV before circumcision, and voluntary testing and counselling services need to be available. Increased uptake of circumcision may cause a shift in the social norm, which might result in stigmatisation of uncircumcised men, who may be seen as less "safe."

A further challenge will be deciding which healthcare providers should be allowed to perform surgery given the dire shortage of trained medical personnel in the developing world. One question is whether only doctors and clinical assistants will be allowed to perform circumcisions, or whether nurses—who are often the only healthcare providers in rural communities—will also be allowed to perform them. Another question is whether health services will work with traditional circumcisers (indigenous practitioners responsible for rites of passage into adulthood or performing circumcision for religious or cultural reasons). Complications of the surgery, principally sepsis, will place an additional burden on healthcare and referral systems.

What impact will implementation of circumcision have on the public sector health service? Many countries of southern Africa—where health services are underdeveloped and overburdened—will have to rethink how nurses provide antenatal care, contraception services, childhood immunisations, and other essential healthcare services. The experience in rolling out antiretroviral therapy can give an idea of the impact on health services in resource poor settings.

While resources from the President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis, and Malaria have successfully secured antiretroviral drugs and created the impetus for the rollout of AIDS care, the limited numbers of healthcare personnel have no spare capacity. Providing circumcision must not compromise the provision of other important components of the routine health service. Careful thought needs to be given to whether a dedicated circumcision programme is warranted and, if so, whether it would be sustainable beyond donor funding.

Young, healthy men are not frequent users of health facilities, except for sexually transmitted diseases. Programmes that integrate safe male circumcision with other sexual and reproductive health services will enhance access to health services for young men, offer HIV testing and counselling, and provide behavioural counselling, treatment for sexually transmitted diseases, health education, and interventions to protect women from violence.

Further research will need to define how to initiate such programmes, test different ways of providing circumcision, develop training programmes, and the mechanisms of supplying the necessary equipment. Important considerations are what factors contribute to uptake, how to monitor and deal with adverse events, and the perceptions and sexual behaviour of individuals and communities.

Given the potential benefit of male circumcision, the UNAIDS/WHO guidance should be implemented in the context of the challenges described above.

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NHS research ethics committees

Still need more common sense and less bureaucracy

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National Health Service research ethics committees exist to ensure that research performed within the NHS complies with recognised ethical standards and to protect the rights, safety, and dignity of all actual or potential participants. In the past decade the operation of research ethics committees has come under, and continues to come under, close scrutiny. Researchers now consider the process of acquiring ethical approval to be so onerous that it is compromising clinical research.[1-3] Medical educators also think that the process is too unwieldy to allow undergraduate students to acquire research experience,[4] an essential learning outcome required by the General Medical Council.[5]

To understand why such dissatisfaction has arisen we need to go back to the early 2000s, when the Central Office for Research Ethics Committees (COREC) was established and the Department of Health issued the *Research Governance Framework for Health and Social Care*.[6] The implementation in 2001 of the European Union Directive 2001/20/EC (the clinical trials directive) forced changes in the system, leading to the introduction of a single application form for multisite applications and a rule that research ethics committees had to respond to applications within 60 days. These changes substantially helped those involved in complex, usually multicentre, studies.

In response to the growing discontent expressed by researchers about the complexity of the research governance process, the Department of Health established an advisory group to review the operation of research ethics committees.[7] Its report confirmed that researchers still perceived the process as too bureaucratic, and its conclusions were sensible and long overdue. These included an immediate recommendation that research ethics committees and research and development departments within trusts should make multiple use of information supplied only once. The review group considered that some research—such as surveys, service evaluation, and research on NHS staff—did not require formal ethical review and proposed the creation of scientific officers who would act in a triage capacity to provide a preliminary assessment of such applications. The response of the Central Office for Research Ethics Committees, *Building on Improvement: Implementing the Recommendation of the Report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees*, was disseminated for consultation last year.[8] The recommendations of the advisory group report[7] have largely been translated into practical and feasible solutions. "Scientific officers" become research ethics advisers, to exist at both a national and local level. Their job will be to provide a rapid review of studies with no untoward ethical implications, to triage applications that require full ethics committee consideration, and to provide educational support to applicants. The central committee acknowledged the need for further improvements in the application form (it is still long, although the latest version has an early filter question to ensure only relevant questions are activated). Was this eventually the spoonful of sugar to make the process of ethical approval more palatable for researchers?

Maybe, but if we look more closely at how the recommendations will be implemented, is there still the potential for sound intentions to be undermined by disproportionate bureaucracy? The research ethics advisers need to be very experienced: the report recommends experience as a chair of an ethics committee. The proposed triage procedure will need piloting, and training requirements will need to be identified. Several levels of filter are suggested from initial review by a coordinator, through to a senior coordinator, then the research ethics adviser, and if necessary, the research ethics committee. Although the report acknowledges that the large volume of undergraduate student applications will not present substantial ethical concerns, it rejects the need for a separate application process or separate system of committees for student projects—recommendations that were suggested in the Doyle report,[9] made in 2004 by a national interprofessional working group. For postgraduate students this seems eminently appropriate, but is this a missed opportunity to streamline undergraduate applications? In the consultation process after release of the recent central committee recommendations,[8] a fast track system for approving low risk studies was wholeheartedly supported by patients, in recognition that this would allow research ethics committees to concentrate their resources more appropriately. In a recent study exploring the impact of research governance on medical students' ability to gain an understanding of research methodology, a fast track application process and the introduction of a specific shortened form were considered the most important strategies to facilitate this aim.[4] Failure to deal with the problem of student research will make it more difficult to ensure coverage of research within the undergraduate curriculum as required by the GMC.[5] Such a lack of academic exposure at undergraduate level will only contribute to the already critical shortage of doctors entering academic medicine.[10 11]

Both medical researchers and teachers support the principles of research governance.[4] The proposed changes to research governance to allow certain research, such as surveys and studies involving NHS staff, to be exempt from research ethics committee review[8] and may rekindle medical teachers' interest in helping undergraduate students gain research experience. *Building on Improvement* provides a longed for opportunity to make research more accessible to all researchers; let us hope it is not too little too late for undergraduate research.